Multicenter Trials – Cardiac MRI in the Clinical Arena

MR-IMPACT:
***M**agnetic **R**esonance **I**maging for **M**yocardial **P**erfusion **A**ssessment in **C**oronary Artery Disease **T**rial*

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Myocardial perfusion assessment by CMR

Contrast media (CM) first-pass techniques are the most commonly used approaches for perfusion-CMR. Alternatively, blood oxygen level dependent (BOLD) techniques and spin-labeling techniques have also been applied to measure myocardial perfusion. The latter two approaches are still in an early experimental stage with rare data in humans and no multicenter data exist. Accordingly, the following description will focus on contrast-enhanced first-pass techniques, and in particular on multicenter results obtained with this technique. Several requirements must be met by this contrast-enhanced first-pass technique in order to generate relevant perfusion information: 1) high temporal resolution of data acquisition (entire data set every 1-2 heart beats) to provide accurate signal intensity – time curves; 2) high spatial resolution in order to differentiate transmural differences in perfusion; 3) adequate cardiac coverage in order to assess extent of disease; 4) CM sensitivity in order to achieve adequate contrast-to-noise (CNR): i.e. T_1 or T_2* weighing corresponding to type and dose of CM. These requirements must be met during hyperemic condition which is typically associated with high heart rates. Therefore, these requirements are satisfied with very fast pulse sequences only.

Pulse sequences for perfusion-CMR

In echo-planar or hybrid echo-planar pulse sequences several k lines are acquired following one single rf excitation reducing the TR per k line down to <2ms. Currently, this pulse design represents the method of choice. In order to reduce motion-induced artefacts, the acquisition windows should ideally be fitted into the cardiac cycle in a way to select phases with minimal motion (e.g. into mid-diastole and/or into mid- to end-systole), while optimising the delay time[1].

In Turbo-Flash (fast low angle shot) pulse sequences the acquisition of each k-line is preceded by an rf excitation, which results in a read-out duration in the order of 350-450ms depending on the number of phase-encoding steps and duration of TR which is typically in the order of several milliseconds.

Steady state free precession sequences yield high signal to noise ratio (SNR) by preservation of magnetization and are therefore of potential benefit. However, combination with magnetization preparation is not trivial with these sequences[2]. Also, spatial encoding is less time-efficient than with hybrid echo-planar pulse sequences.

Parallel imaging approaches are attractive, since they allow for shortening the acquisition window by a factor of 2-4. However, a disadvantage is its reduced SNR given by the square root of the acceleration factor times the geometry factor. Further studies are needed to determine, whether or not the advantage of a shorter acquisition window, which is likely to reduce motion-induced artefacts, is offset by a reduced SNR.

Magnetization preparation for T_1-shortening CM

Typically, the read-out is prepared by a 90º saturation pulse with recovery times as short as 100-150 ms. When combined with a hybrid echo-planar pulse sequence the data acquisition window can be as short as 200-300 ms/slice allowing for multislice data acquisition at a high sampling rate, i.e. a complete stack of images is acquired every 1-2 heart beats[1,3]. This preparation scheme has replaced the inversion recovery (IR)-approach at most sites. With the IR-technique the recovery time is set to null the signal of normal myocardium and is typically in the range of 300-400ms. Thus, combining an IR- preparation scheme with a turbo-FLASH readout would result in a total data acquisition window of 650-750ms/slice[4].

Contrast media for perfusion-CMR

T_1-shortening extravascular Gadolinium-based CM are most commonly used for MR first pass perfusion imaging. These CM are injected as a bolus in a peripheral (antecubital) vein in dosages of 0.025[4] to 0.15[3,5] mmol/kg body weight at rates of 3-8 ml/sec. During CM administration signal intensity changes in the right and left ventricular cavities and finally in the left ventricular myocardium are monitored using one of the above mentioned pulse sequences. The increase in signal during first pass that is achieved in the left ventricular myocardium depends on the dose and dispersion of the CM bolus and also on the type of the pulse sequence. It appears crucial to induce a signal increase that is far higher than the noise floor in the images in order to be able to differentiate normally perfused myocardium from areas of hypoperfusion[6]. From single center[1,6] and multicenter trials[3,7], there is a trend towards better diagnostic performance at higher doses of CM for stress-only protocols.

Limited data are available for the application of intravascular Gd-based CM for myocardial perfusion imaging[8]. To become an intravascular agent many Gd-ions are bound to larger molecules such as albumin[8] or dendrimers[9]. With these types of CM signal intensity increase in the myocardium is expected to be lower (at a given Gd-ion concentration) since these CM confined to the intravascular space will address fewer protons than an extravascular CM which extravasates from the vascular compartment during first-pass[10,11]. Moreover, perfusion modelling also has to consider water proton exchange between the intra- and extravascular compartment, leakage in territories of ischemia, and vascular architecture (for more details see also reference[12]). As to our knowledge, no multicenter data are available for intravascular CM so far.

Stress-only versus stress-rest protocol

Another open question is relating to the procotol being a stress-only protocol or a stress-rest protocol. In the stress-rest protocol, coronary flow reserve (CFR) is calculated by dividing hyperemic stress perfusion by resting perfusion. This approach therefore, requires parameters which must be linearly related to perfusion over a wide range of flow values covering resting flow (approximately 1ml/min/g) and hyperemic flow (as high as 4-5ml/min/g). Since the upslope is non-linearly related with high flow rates[1,13], this parameter appears suboptimal for a CFR approach and quantitative perfusion measurements (considering the arterial input function) are most likely the ones that will ultimately fullfill the requirements for the CFR approach. Applying a stress-only protocol appears advantages, since perfusion in myocardial regions supplied by hemodynamically relevant stenoses (blunting hyperemic flow response with resulting perfusion of approximately 1ml/min/g) is compared with normally perfused, i.e. hyperemic myocardium (allowing perfusion in the range of 2-5ml/min/g). Thus, a stress-only protocol differentiates low perfusion (approximately 1ml/min/g or lower in the case of steal) with very high flows, rendering this approach less sensitive for non-linearity. A stress-only protocol in a multicenter design yielded high sensitivities and specificities of 93% and 75%, respectively, for pooled data of groups with 0.1 and 0.15mmol/kg CM[3]. To our knowledge, no multicenter trials are available so far assessing the CFR approach for detection of coronary artery disease (CAD).

In a stress-only approach, a combination with delayed enhancement MR imaging for detection of scar tissue[14,15] appears reasonable in analogy to the stress-injection and rest-injection for re-distribution in SPECT imaging. It would be mentioned here, that both, rest injections of MR and SPECT exploit CM redistribution for viability/scar discrimination (the MR CM redistribute into the interstitial space of scar tissue, while radioactive CM redistritbute into viable myocytes resulting in high signal and “cold spots” for scar tissue, respectively).

Data analysis

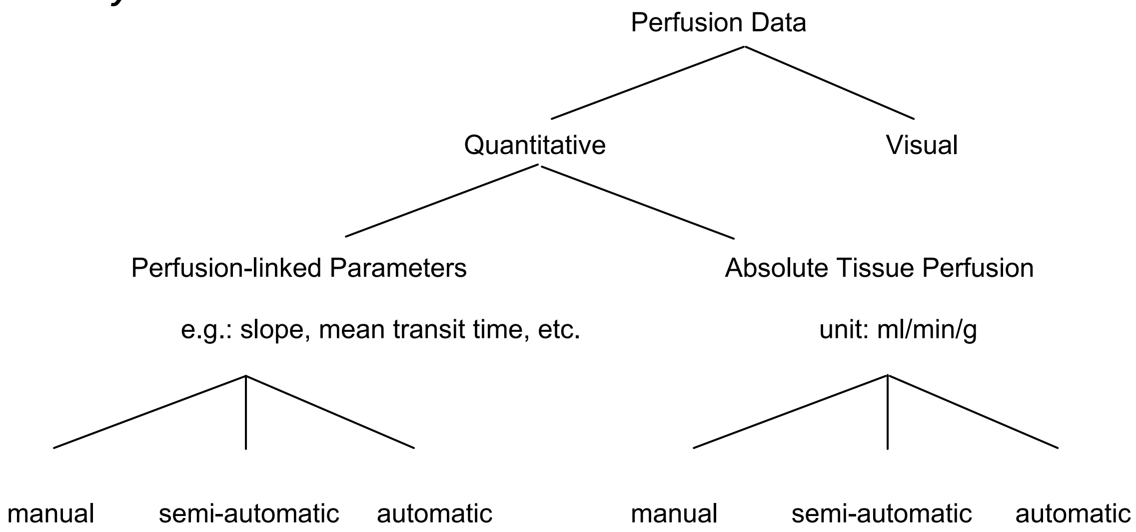
Visual versus quantitative analyses

To increase reproducibility and reduce observer-dependence semi-automatic or automatic analysis procedures for MR perfusion data sets are preferable over manual analysis approaches. A multicenter study employed a visual reading and interreader agreement was rather poor with kappa-values ranging from 0.30 to 0.35 for doses of 0.10 and 0.15, respectively[5]. In contrast, quantitative analyses yield numbers for perfusion parameters derived from the signal intensity – time curves. These parameters are extracted from the data set manually (with observer-interaction with the data), semiautomatically (with reduced observer-interaction), or fully automatically (eliminating any observer-interaction). It is obvious, that the latter approaches, i.e. semi-automatic or fully automatic analyses, are dependent upon adequate to excellent data quality. While experts can judge image artefacts and “overread” them, such a visual approach or eyeball guessing is traded for considerable reader-variability in relation to degradation of data and level of reader experience. In a multicenter single-vendor study, a semi-automatic quantitative approach was applied (i.e. upslope calcuation) which yielded a high kappa-value of 0.73 with an area under the receiver operator characteristics (ROC) curve for detection of CAD of 0.86[3].

Therefore, for data of adequate quality, a quantitative approach involving a semi-automatic or automatic data extraction, would be clearly advantageous.

The extracted parameters then are either linked to tissue perfusion or represent perfusion in absolute units of ml/min/g tissue. The upslope parameter proposed more than 10 years ago[16] yielded good results in single center[1] and mutlicenter trials[3] so far. Nevertheless, considerable efforts are still needed to clarify the question, which perfusion-linked parameters finally will yield best performance for the detection of CAD. For the performance of absolute perfusion measurements no multicenter data are available so far.

Data analysis:



Diagnostic performance of MR perfusion imaging:

A study published by our institution[1] using a multislice approach and a peripheral injection of a Gadolinium-based CM yielded a sensitivity and specificity of 91% and 94%, respectively, for detection of patients with hemodynamically significant coronary artery stenoses defined as reduced CFR by ^{13}N-ammonia PET. Sensitivity and specificity for detection of morphologically defined CAD (≥1coronary artery with ≥50% diameter stenosis in quantitative coronary angiography) were 87% and 85%, respectively (area under the ROC curve: 0.91). These single center results were recently confirmed by a multi-center trial applying a visual reading[5]. Another approach evaluated the potential of semi-automatic analysis of perfusion data for detection of CAD defined as ≥50% diameter stenosis on quantitative coronary angiography[3]. In this multicenter study the slope of the signal intensity – time curve as a perfusion-linked parameter was analyzed and a sensitivity and specificity of 93% and 75% was achieved, respectively, with an area under the ROC curve of 0.88, confirming the slope results of the single center study presented earlier (area under the ROC curve: 0.91[1]).

Even larger multi-vendor multi-center Phase II and III clinical trials are currently ongoing. One of these is known as the ***MR-IMPACT*** programme (***M***agnetic ***R***esonance ***I***maging for ***M***yocardial ***P***erfusion ***A***ssessment in ***C***oronary Artery Disease ***T***rial). The phase II (dose finding) study of MR-IMPACT involving 234 patients studied in 18 centers world-wide has recently been finalized and was presented at the Annual Meeting of the European Society of Cardiology, Stockholm, 2005. It could confirm single-center and single-vendor multi-center trials, and in particular yielded results superior to SPECT imaging[7]. Detailed results of MR-IMPACT are currently in preparation for publication.

Future perspectives and clinical implications

As demonstrated by a substantial number of single center studies and recently by large multicenter studies, perfusion-CMR may become a first-line modality in the work-up of patients with known or suspected CAD in the near future. Moreover, multicenter trials ongoing and in preparation will address some remaining issues such as the type of the imaging protocol (stress-only versus stress-rest protocols), data analysis, quality criteria, and others. In experienced centers, perfusion-CMR can be recommended as an alternative to SPECT imaging for the detection of CAD. In patients with wall motion abnormalities, the combined approach of perfusion-CMR and late-enhancement CMR appears particularly attractive for a comprehensive work-up of cardiac patients.

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